Use of vasopressors and inotropes

Author: Scott Manaker, MD, PhD
Section Editor: Polly E Parsons, MD
Deputy Editor: Geraldine Finlay, MD

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Sep 2016. | This topic last updated: Sep 13, 2016.

INTRODUCTION — Vasopressors are a powerful class of drugs that induce vasoconstriction and thereby elevate mean arterial pressure (MAP). Vasopressors differ from inotropes, which increase cardiac contractility; however, many drugs have both vasopressor and inotropic effects. Although many vasopressors have been used since the 1940s, few controlled clinical trials have directly compared these agents or documented improved outcomes due to their use [1]. Thus, the manner in which these agents are commonly used largely reflects expert opinion, animal data, and the use of surrogate end points, such as tissue oxygenation, as a proxy for decreased morbidity and mortality.

Basic adrenergic receptor physiology and the principles, complications, and controversies surrounding use of vasopressors and inotropes for treatment of shock are presented here. Issues related to the differential diagnosis of shock and the use of vasopressors in patients with septic shock are discussed separately. (See "Definition, classification, etiology, and pathophysiology of shock in adults" and "Evaluation and management of suspected sepsis and septic shock in adults".)

RECEPTOR PHYSIOLOGY — The main categories of adrenergic receptors relevant to vasopressor activity are the alpha-1, beta-1, and beta-2 adrenergic receptors, as well as the dopamine receptors [2,3].

Alpha adrenergic — Activation of alpha-1 adrenergic receptors, located in vascular walls, induces significant vasoconstriction. Alpha-1 adrenergic receptors are also present in the heart and can increase the duration of contraction without increased chronotropy. However, clinical significance of this phenomenon is unclear [4].

Beta adrenergic — Beta-1 adrenergic receptors are most common in the heart and mediate increases in inotropy and chronotropy with minimal vasoconstriction. Stimulation of beta-2 adrenergic receptors in blood vessels induces vasodilation.

Dopamine — Dopamine receptors are present in the renal, splanchnic (mesenteric), coronary, and cerebral vascular beds; stimulation of these receptors leads to vasodilation. A second subtype of dopamine receptors causes vasoconstriction by inducing norepinephrine release.

PRINCIPLES — Hypotension may result from hypovolemia (eg, exsanguination), pump failure (eg, severe medically refractory heart failure or shock complicating myocardial infarction), or a pathologic maldistribution of blood flow (eg, septic shock, anaphylaxis). (See "Definition, classification, etiology, and pathophysiology of shock in adults" and "Inotropic agents in heart failure due to systolic dysfunction".)

Vaspressors are indicated for a decrease of >30 mmHg from baseline systolic blood pressure, or a mean arterial pressure <60 mmHg when either condition results in end-organ dysfunction due to hypoperfusion. Hypovolemia should be corrected prior to the institution of vasopressor therapy [5]. (See "Treatment of severe hypovolemia or hypovolemic shock in adults".)

The rational use of vasopressors and inotropes is guided by three fundamental concepts:

- One drug, many receptors – A given drug often has multiple effects because of actions upon more than one receptor. As an example, dobutamine increases cardiac output by beta-1 adrenergic receptor

https://www.uptodate.com/contents/use-of-vasopressors-and-inotropes#print?source=search_result&search=vasopressors&selectedTitle=1~150
activation; however, it also acts upon beta-2 adrenergic receptors and thus induces vasodilation and can cause hypotension.

- Dose-response curve – Many agents have dose-response curves, such that the primary adrenergic receptor subtype activated by the drug is dose-dependent. As an example, dopamine stimulates beta-1 adrenergic receptors at doses of 2 to 10 mcg/kg per minute, and alpha adrenergic receptors when doses exceed 10 mcg/kg per minute.

- Direct versus reflex actions – A given agent can affect mean arterial pressure (MAP) both by direct actions on adrenergic receptors and by reflex actions triggered by the pharmacologic response. Norepinephrine-induced beta-1 adrenergic stimulation alone normally would cause tachycardia. However, the elevated MAP from norepinephrine's alpha-adrenergic receptor-induced vasoconstriction results in a reflex decrease in heart rate. The net result may be a stable or slightly reduced heart rate when the drug is used.

**PRACTICAL ISSUES** — Use of vasopressors and inotropic agents requires attention to a number of issues:

**Volume resuscitation** — Repletion of adequate intravascular volume, when time permits, is crucial prior to the initiation of vasopressors. As an example, most patients with septic shock require at least 2 liters of intravenous fluid in order for vasopressors to be maximally effective [6]. Vasopressors will be ineffective or only partially effective in the setting of coexistent hypovolemia.

Fluids may be withheld in patients with significant pulmonary edema due to the acute respiratory distress syndrome (ARDS) or heart failure (HF). In patients with a pulmonary artery catheter, pulmonary capillary wedge pressures (PCWP) of 18 to 24 mmHg are recommended for cardiogenic shock [7], and 12 to 14 mmHg for septic or hypovolemic shock [8]. (See "Pulmonary artery catheterization: Interpretation of hemodynamic values and waveforms in adults").

**Selection and titration** — Choice of an initial agent should be based upon the suspected underlying etiology of shock (eg, dobutamine in cases of cardiac failure without significant hypotension, epinephrine for anaphylactic shock). The dose should be titrated up to achieve effective blood pressure or end-organ perfusion as evidenced by such criteria as urine output or mentation. If maximal doses of a first agent are inadequate, then a second drug should be added to the first. In situations where this is ineffective, such as refractory septic shock, anecdotal reports describe adding a third agent, although no controlled trials have demonstrated the utility of this approach.

**Route of administration** — Vasopressors and inotropic agents should be administered through an appropriately positioned central venous catheter, if available. This facilitates more rapid delivery of the agent to the heart for systemic distribution and eliminates the risk of peripheral extravasation. When a patient does not have a central venous catheter, vasopressors and inotropic agents can be administered through an appropriately positioned peripheral intravenous catheter temporarily, until a central venous catheter is inserted. (See "Complications of central venous catheters and their prevention" and "Overview of central venous access").

**Tachyphylaxis** — Responsiveness to these drugs can decrease over time due to tachyphylaxis. Doses must be constantly titrated to adjust for this phenomenon and for changes in the patient's clinical condition [9,10].

**Hemodynamic effects** — Mean arterial pressure (MAP) is influenced by systemic vascular resistance (SVR) and cardiac output (CO). In situations such as cardiogenic shock, elevating SVR increases afterload and the work of an already failing heart, thus potentially lowering CO. Some authors recommend keeping the SVR approximately 700 to 1000 dynes x sec/cm² to avoid excessive afterload and to minimize complications from profound vasoconstriction (calculator 1) [11]. However, there is no consensus regarding an ideal target cardiac index (CI). Studies that have attempted to maintain a supraphysiologic CI of >4 to 4.5 L/minute per m² have not shown consistent benefit [12,13]. (See "Oxygen delivery and consumption").
Subcutaneous delivery of medications — Critically ill patients often receive subcutaneously injected medications, such as heparin and insulin. The bioavailability of these medications can be reduced during treatment with vasopressors due to cutaneous vasoconstriction.

This was demonstrated in a study that monitored plasma factor Xa levels in three groups of hospitalized patients following the initiation of prophylactic low molecular weight heparin \[^{14}\]. Patients who required vasopressor support (dopamine >10 mcg/kg per minute, norepinephrine >0.25 mcg/kg per minute, or phenylephrine >2 mcg/kg per minute) had decreased factor Xa activity compared to both intensive care unit (ICU) patients who did not require vasopressors and routine postoperative control patients. The clinical significance of the decrease in plasma factor Xa levels was not determined.

The authors of the study suggested that patients might need higher doses of LMW heparin to attain adequate thrombosis prophylaxis. Another approach is to change subcutaneous medications to an intravenous form whenever a patient is receiving vasopressor therapy.

Frequent re-evaluation — Critically ill patients may undergo a second hemodynamic insult which necessitates a change in vasopressor or inotrope management. The dosage of a given agent should not simply be increased because of persistent or worsening hypotension without reconsideration of the patient’s clinical situation and the appropriateness of the current strategy.

ADRENERGIC AGENTS — Adrenergic agents, such as phenylephrine, norepinephrine, dopamine, and dobutamine, are the most commonly used vasopressor and inotropic drugs in critically ill patients (table 1). These agents manifest different receptor selectivity and clinical effects (table 2).

Norepinephrine — Norepinephrine (Levophed) acts on both alpha-1 and beta-1 adrenergic receptors, thus producing potent vasoconstriction as well as a modest increase in cardiac output \[^{5}\]. A reflex bradycardia usually occurs in response to the increased mean arterial pressure (MAP), such that the mild chronotropic effect is canceled out and the heart rate remains unchanged or even decreases slightly. Norepinephrine is the preferred vasopressor for the treatment of septic shock. (See ‘Choice of agent in septic shock’ below and “Evaluation and management of suspected sepsis and septic shock in adults”.)

Phenylephrine — Phenylephrine (Neo-Synephrine) has purely alpha-adrenergic agonist activity and therefore results in vasoconstriction with minimal cardiac inotropy or chronotropy. MAP is augmented by raising systemic vascular resistance (SVR) \[^{15}\]. The drug is useful in the setting of hypotension with an SVR <700 dynes x sec/cm\(^5\) (eg, hyperdynamic sepsis, neurologic disorders, anesthesia-induced hypotension). A potential disadvantage of phenylephrine is that it may decrease stroke volume, so it is reserved for patients in whom norepinephrine is contraindicated due to arrhythmias or who have failed other therapies \[^{16}\].

Although SVR elevation increases cardiac afterload, most studies document that cardiac output (CO) is either maintained or actually increased among patients without pre-existing cardiac dysfunction \[^{4,17}\]. The drug is contraindicated if the SVR is >1200 dynes x sec/cm\(^5\).

Epinephrine — Epinephrine (Adrenalin) has potent beta-1 adrenergic receptor activity and moderate beta-2 and alpha-1 adrenergic receptor effects. Clinically, low doses of epinephrine increase CO because of the beta-1 adrenergic receptor inotropic and chronotropic effects, while the alpha adrenergic receptor-induced vasoconstriction is often offset by the beta-2 adrenergic receptor vasodilation. The result is an increased CO, with decreased SVR and variable effects on the MAP \[^{3}\]. However, at higher epinephrine doses the alpha-adrenergic receptor effect predominates, producing increased SVR in addition to an increased CO. Epinephrine is most often used for the treatment of anaphylaxis, as a second line agent (after norepinephrine) in septic shock, and for management of hypotension following coronary artery bypass grafting.

Other disadvantages of epinephrine include dysrhythmias (due to beta-1 adrenergic receptor stimulation) and splanchnic vasoconstriction. The degree of splanchnic vasoconstriction appears to be greater with epinephrine than with equipotent doses of norepinephrine or dopamine in patients with severe shock \[^{18}\], although the clinical importance of this is unclear \[^{16}\].

Ephedrine — Similar to epinephrine, ephedrine acts primarily on alpha- and beta-adrenergic receptors, but with less potency. It also has an effect by leading to release of endogenous norepinephrine. Ephedrine is rarely used except in the setting of post-anesthesia-induced hypotension.

Dopamine — Dopamine (Intropin) has a variety of effects depending upon the dose range administered. It is most often used as a second-line alternative to norepinephrine in patients with absolute or relative bradycardia and a low risk of tachyarrhythmias. Weight-based administration of dopamine can achieve quite different serum drug concentrations in different individuals [19], but the following provides an approximate description of effects:

- At doses of 1 to 2 mcg/kg per minute, dopamine acts predominantly on dopamine-1 receptors in the renal, mesenteric, cerebral, and coronary beds, resulting in selective vasodilation. Some reports suggest that dopamine increases urine output by augmenting renal blood flow and glomerular filtration rate, and natriuresis by inhibiting aldosterone and renal tubular sodium transport [20-22]. These effects may be blunted by haloperidol and other butyrophenones [22]. However, the clinical significance of these phenomena is unclear, and some patients may develop hypotension at these low doses [23]. (See "Renal actions of dopamine").

- At 5 to 10 mcg/kg per minute, dopamine also stimulates beta-1 adrenergic receptors and increases cardiac output, predominantly by increasing stroke volume with variable effects on heart rate [24]. Doses between 2 and 5 mcg/kg per minute have variable effects on hemodynamics in individual patients: vasodilation is often balanced by increased stroke volume, producing little net effect upon systemic blood pressure. Some mild alpha adrenergic receptor activation increases SVR, and the sum of these effects is an increase in MAP.

- At doses >10 mcg/kg per minute, the predominant effect of dopamine is to stimulate alpha-adrenergic receptors and produce vasoconstriction with an increased SVR [24,25]. However, the overall alpha-adrenergic receptor effect of dopamine is weaker than that of norepinephrine, and the beta-1 adrenergic receptor stimulation of dopamine at doses >2 mcg/kg per minute can result in dose-limiting dysrhythmias.

In practical terms, the dose-dependent effects of dopamine mean that changing the dose of the drug is akin to switching vasopressors. Conversely, simply increasing the dose of dopamine without being cognizant of the different receptor populations activated can cause untoward results.

The usual dose range for dopamine is 2 to 20 mcg/kg per minute, although doses as high as 130 mcg/kg per minute have been employed [26]. When used for cardiac failure, dopamine should be started at 2 mcg/kg per minute and then titrated to a desired physiologic effect rather than depending on the predicted pharmacologic ranges described above.

Dobutamine — Dobutamine (Dobutrex) is not a vasopressor but rather is an inotrope that causes vasodilation. Dobutamine’s predominant beta-1 adrenergic receptor effect increases inotropy and chronotropy and reduces left ventricular filling pressure. In patients with heart failure this results in a reduction in cardiac sympathetic activity [27]. However, minimal alpha- and beta-2 adrenergic receptor effects result in overall vasodilation, complemented by reflex vasodilation to the increased CO. The net effect is increased CO, with decreased SVR with or without a small reduction in blood pressure.

Dobutamine is most frequently used in severe, medically refractory heart failure and cardiogenic shock and should not be routinely used in sepsis because of the risk of hypotension. Dobutamine does not selectively vasodilate the renal vascular bed, as dopamine does at low doses. (See "Inotropic agents in heart failure due to systolic dysfunction").

Isoproterenol — Isoproterenol (Isuprel) also is primarily an inotropic and chronotropic agent rather than a vasopressor. It acts upon beta-1 adrenergic receptors and, unlike dobutamine, has a prominent chronotropic effect. The drug’s high affinity for the beta-2 adrenergic receptor causes vasodilation and a decrease in MAP.
Therefore, its utility in hypotensive patients is limited to situations in which hypotension results from bradycardia.

**Contraindications and interactions** — Several conditions or medications require avoidance of specific agents:

- In patients with cardiogenic shock, norepinephrine is preferred over dopamine as the first-line vasopressor because a subgroup analysis from a randomized trial found that patients with cardiogenic shock who received dopamine had a higher mortality than those who received norepinephrine [16,28]. In addition, dysrhythmias were more common in the dopamine group.

- Patients with pheochromocytoma are at risk of excessive autonomic stimulation from adrenergic vasopressors.

- **Dobutamine** is contraindicated in the setting of idiopathic hypertrophic subaortic stenosis.

- Patients receiving monoamine oxidase inhibitors are extremely sensitive to vasopressors and, therefore, require much lower doses.

**VASOPRESSIN AND ANALOGS** — Vasopressin (antidiuretic hormone) is used in the management of diabetes insipidus and esophageal variceal bleeding; however, it may also be helpful in the management of vasodilatory shock (Table 1). Although its precise role in vasodilatory shock remains to be defined, it is primarily used as a second-line agent in refractory vasodilatory shock, particularly septic shock or anaphylaxis that is unresponsive to epinephrine [29-34]. It is also used occasionally to reduce the dose of the first-line agent. Terlipressin, a vasopressin analog, has been assessed in patients with vasodilatory shock [35-40], but it is not available in the United States.

The effects of vasopressin and terlipressin in vasodilatory shock (mostly septic shock) were evaluated in a systematic review that identified 10 relevant randomized trials (1134 patients) [41]. A meta-analysis of six of the trials (512 patients) compared vasopressin or terlipressin with placebo or supportive care. There was no significant improvement in short-term mortality among patients who received either vasopressin or terlipressin (40.2 versus 42.9 percent, relative risk 0.91, 95% CI 0.79-1.05). However, patients who received vasopressin or terlipressin required less norepinephrine. A second randomized trial compared vasopressin with norepinephrine in 409 patients with septic shock. Although vasopressin did not improve mortality or the number of kidney failure-free days, it may have been associated with a reduction in the rate of kidney failure requiring renal replacement therapy (25 versus 35 percent) [42]. Further studies are needed before vasopressin can replace norepinephrine as the first-choice agent for those with septic shock. (See ‘Choice of agent in septic shock’ below.)

The effects of vasopressin may be dose dependent. A randomized trial compared two doses of vasopressin (0.0333 versus 0.067 IU/min) in 50 patients with vasodilatory shock who required vasopressin as a secondpressor agent [43]. The higher dose was more effective at increasing the blood pressure without increasing the frequency of adverse effects in these patients. However, doses of vasopressin above 0.03 units/min have been associated with coronary and mesenteric ischemia and skin necrosis in other studies [16,44-47] and are avoided unless an adequate mean arterial pressure (MAP) cannot be attained with other vasopressor agents.

Rebound hypotension appears to be common following withdrawal of vasopressin. To avoid rebound hypotension, the dose is slowly tapered by 0.01 units/min every 30 minutes.

Other potential adverse effects of vasopressin include hyponatremia and pulmonary vasoconstriction [16,44-47]. Terlipressin appears to have a similar side effect profile to vasopressin. In a meta-analysis of four trials (431 patients) that was conducted as part of the systematic review described above, there was no significant difference in the frequency of adverse events among patients who received either vasopressin or terlipressin (10.6 versus 11.8 percent, relative risk 0.90, 95% CI 0.49-1.67) [41].
NONADRENERGIC AGENTS — A number of agents produce vasoconstriction or inotropy through nonadrenergic mechanisms, including phosphodiesterase inhibitors and nitric oxide synthase inhibitors (table 1).

**PDE inhibitors** — Phosphodiesterase (PDE) inhibitors, such as inamrinone (formerly known as amrinone) and milrinone, are nonadrenergic drugs with inotropic and vasodilatory actions. In many ways, their effects are similar to those of dobutamine but with a lower incidence of dysrhythmias. PDE inhibitors most often are used to treat patients with impaired cardiac function and medically refractory heart failure, but their vasodilatory properties limit their use in hypotensive patients [24]. (See "Inotropic agents in heart failure due to systolic dysfunction").

**NOS inhibitors** — Nitric oxide overproduction appears to play a major role in vasodilation induced by sepsis (see "Pathophysiology of sepsis"). Studies of nitric oxide synthase (NOS) inhibitors such as N-monomethyl-L-arginine (L-NMMA) in sepsis demonstrate a dose-dependent increase in systemic vascular resistance (SVR) [48]. However, cardiac index (CI) and heart rate (HR) decrease, even when patients are treated concomitantly with norepinephrine or epinephrine. The increase in SVR tends to be offset by the drop in CI, such that mean arterial pressure (MAP) is only minimally augmented. The clinical utility of this class of drugs remains unproven.

**COMPLICATIONS** — Vasopressors and inotropic agents have the potential to cause a number of significant complications, including hypoperfusion, dysrhythmias, myocardial ischemia, local effects, and hyperglycemia. In addition, a number of drug interactions exist.

**Hypoperfusion** — Excessive vasoconstriction in response to hypotension and vasopressors can produce inadequate perfusion of the extremities, mesenteric organs, or kidneys. Excessive vasoconstriction with inadequate perfusion, usually with an systemic vascular resistance (SVR) >1300 dynes x sec/cm$^5$, commonly occurs in the setting of inadequate cardiac output or inadequate volume resuscitation.

The initial findings are dusky skin changes at the tips of the fingers and/or toes, which may progress to frank necrosis with autoamputation of the digits. Compromise of the renal vascular bed may produce renal insufficiency and oliguria, while patients with underlying peripheral artery disease may develop acute limb ischemia.

Inadequate mesenteric perfusion increases the risk of gastritis, shock liver, intestinal ischemia, or translocation of gut flora with resultant bacteremia. Despite these concerns, maintenance of MAP with vasopressors appears more effective in maintaining renal and mesenteric blood flow than allowing the MAP to drop, and maintenance of MAP with vasopressors may be life-saving despite evidence of localized hypoperfusion [15,49].

**Dysrhythmias** — Many vasopressors and inotropes exert powerful chronotropic effects via stimulation of beta-1 adrenergic receptors. This increases the risk of sinus tachycardia (most common), atrial fibrillation (potentially with increased atrioventricular nodal [A-V] conduction and therefore an increased ventricular response), re-entrant atrioventricular node tachycardia, or ventricular tachyarrhythmias.

Adequate volume loading may minimize the frequency or severity of dysrhythmias. Despite this, dysrhythmias often limit the dose and necessitate switching to another agent with less prominent beta-1 effects. The degree to which the agent affects the frequency of dysrhythmias was illustrated by a randomized trial of 1679 patients with shock [28]. Dysrhythmias were significantly more common among patients who received dopamine than among those who received norepinephrine (24.1 versus 12.4 percent).

**Myocardial ischemia** — The chronotropic and inotropic effects of beta-adrenergic receptor stimulation can increase myocardial oxygen consumption. While there is usually coronary vasodilation in response to vasopressors [50], perfusion may still be inadequate to accommodate the increased myocardial oxygen demand. Daily electrocardiograms on patients treated with vasopressors or inotropes may screen for occult
ischemia, and excessive tachycardia should be avoided because of impaired diastolic filling of the coronary arteries.

**Local effects** — Peripheral extravasation of vasopressors into the surrounding connective tissue can lead to excessive local vasoconstriction with subsequent skin necrosis. To avoid this complication, vasopressors should be administered via a central vein whenever possible. If infiltration occurs, local treatment with phentolamine (5 to 10 mg in 10 mL of normal saline) injected subcutaneously can minimize local vasoconstriction [51].

**Hyperglycemia** — Hyperglycemia may occur due to the inhibition of insulin secretion. The magnitude of hyperglycemia generally is minor and is more pronounced with norepinephrine and epinephrine than dopamine [21]. Monitoring of blood glucose while on vasopressors can prevent complications of untreated hyperglycemia.

**CONTROVERSIES** — Several controversies exist regarding the use of vasopressors and inotropic agents in critically ill patients. Most stem from the relative paucity of large-scale studies comparing similar patient populations treated with different regimens. The development of clear definitions for the systemic inflammatory response syndrome, sepsis, and septic shock is a step forward toward comparative trials among standardized patient populations. (See "Sepsis syndromes in adults: Epidemiology, definitions, clinical presentation, diagnosis, and prognosis".)

**Choice of agent in septic shock** — The optimal agent in patients with septic shock is unknown and practice varies considerably among experts. However, based upon meta-analyses of small randomized trials and observational studies, a paradigm shift in practice has occurred such that most experts prefer to avoid dopamine in this population and favor norepinephrine as the first-choice agent.

- **First-line agent** – Data that support norepinephrine as a first-line agent in septic shock are derived from numerous trials that have compared one vasopressor to another in septic shock [11,28,49,52-55]. These trials included norepinephrine versus phenylephrine [56], norepinephrine versus vasopressin [42,57-59], norepinephrine versus terlipressin [35,60], norepinephrine versus epinephrine [61], and vasopressin versus terlipressin [62]. While some of the comparisons found no convincing difference in mortality, length of stay in the ICU or hospital, or incidence of kidney failure [42,63], two 2012 meta-analyses have reported increased mortality among patients who received dopamine during septic shock compared to those who received norepinephrine (53 to 54 percent versus 48 to 49 percent) [52,64]. Although the causes of death in the two groups were not directly compared, both meta-analyses identified arrhythmic events were about twice as common with dopamine than norepinephrine.

  However, the initial choice of vasopressor in patients with sepsis is often individualized and determined by additional factors including the presence or absence of coexistent etiologies or conditions contributing shock. For example, in patients with septic shock associated with a high cardiac output (also known as "hyperdynamic" septic shock or "warm" sepsis) who also have significant tachycardia (eg, fast atrial fibrillation, sinus tachycardia >160/minute) or in those who develop tachycardia with norepinephrine, agents that completely lack beta adrenergic effects (eg, phenylephrine, vasopressin) may be preferred. This preference is based upon the rationale that the predominant physiological abnormality is low systemic vascular resistance and the addition of agents with any beta adrenergic activity may worsen tachycardia and prompt further decompensation.

- **Second-line agent** – The addition of a second agent may be required and, again, should be individualized taking into account the patient’s clinical status (eg, the presence of heart failure, tachycardia, arrhythmias, additional etiologies for shock, underlying ischemia). For example, vasopressin or terlipressin may be beneficial, when added to other vasopressor agents, such as norepinephrine [16]. In contrast, these agents should be avoided in those with active organ ischemia. As another example, for patients with refractory septic shock associated with a low cardiac output (also known as “hypodynamic” septic shock
or “cold” sepsis), an inotropic agent is often added to norepinephrine; we typically add epinephrine, although dobutamine is an alternative. (See 'Epinephrine' above and 'Dobutamine' above.)

- Third-line agent – For patients who remain hypotensive despite two vasopressors, there is no evidence that adding a third vasopressor is superior to trying an alternative combination of vasopressors (ie, switching from norepinephrine plus vasopressin to norepinephrine plus phenylephrine).

"Renal dose" dopamine — Dopamine selectively increases renal blood flow when administered to normal volunteers at 1 to 3 mcg/kg per minute [65,66]. Animal studies also suggest that low-dose dopamine in the setting of vasopressor-dependent sepsis helps preserve renal blood flow [67]. (See "Renal actions of dopamine" and "Possible prevention and therapy of postischemic (ischemic) acute tubular necrosis".)

However, a beneficial effect of low or "renal dose" dopamine is less proven in human patients with sepsis or other critical illness. Critically ill patients who do not have evidence of renal insufficiency or decreased urine output will develop a diuresis in response to dopamine at 2 to 3 mcg/kg per minute, with variable effects on creatinine clearance, but the benefit of this diuresis is questionable [9,23]. The intervention is not entirely benign because hypotension and tachycardia may ensue. One small study demonstrated that the addition of low dose dopamine to patients receiving other vasopressors increases splanchnic blood flow but does not alter other indices of mesenteric perfusion, such as gastric intramucosal pH (pHi) [68].

At present, there are no data to support the routine use of low dose dopamine to prevent or treat acute renal failure or mesenteric ischemia. In general, the most effective means of protecting the kidneys in the setting of septic shock appears to be the maintenance of mean arterial pressure (MAP) >60 mmHg while attempting to avoid excessive vasoconstriction (ie, the systemic vascular resistance [SVR] should not exceed 1300 dynes x sec/cm$^5$) [6,11,69,70].

Optimal dosage — Several studies have suggested improved tissue perfusion when higher doses of norepinephrine (up to 350 mcg/min) are used [11,70]. However, no survival benefit of high-dose norepinephrine has been conclusively proven.

Supranormal cardiac index — Elevation of the cardiac index with inotropic agents to supranormal values (ie, >4.5 L/minute per m$^2$) potentially increases oxygen delivery to peripheral tissues. In theory, increased oxygen delivery may prevent tissue hypoxia and improve outcomes, and initial studies appeared to support this hypothesis [71-73]. However, later larger trials showed that goal-oriented hemodynamic therapy to increase either cardiac index to >4.5 L/min per m$^2$ or oxygen delivery to >600 to 650 mL/min per m$^2$ with volume expansion or dobutamine resulted in either no improvement or worsened morbidity or mortality [12,13,74]. Therefore, the routine administration of vasopressors or inotropes to improve cardiac output or oxygen delivery to supranormal levels is not advocated. (See "Oxygen delivery and consumption".)

The American Thoracic Society (ATS) statement on the detection, correction, and prevention of tissue hypoxia, as well as other ATS guidelines, can be accessed through the ATS web site at www.thoracic.org/statements.

SUMMARY AND RECOMMENDATIONS

- Vasopressors are a powerful class of drugs that induce vasoconstriction and elevate mean arterial pressure (MAP). (See 'Introduction' above.)

- Alpha-1 adrenergic receptors induce vasoconstriction, while beta-1 receptors induce inotropy plus chronotropy, and beta-2 receptors induce vasodilation. One subtype of dopamine receptor induces norepinephrine release with subsequent vasoconstriction, although many dopamine receptors induce vasodilation. (See 'Receptor physiology' above.)

- Vasopressors are indicated for a MAP <60 mmHg, or a decrease of systolic blood pressure that exceeds 30 mmHg from baseline, when either condition results in end-organ dysfunction due to hypoperfusion. (See 'Principles' above.)
● Hypovolemia should be corrected prior to the institution of vasopressor therapy for maximum efficacy. Patients should be re-evaluated frequently once vasopressor therapy has been initiated. Common issues that arise include tachyphylaxis, which may require dose titration, and additional hemodynamic insults, which should be recognized and managed. (See 'Practical Issues' above.)

● Choice of an initial agent should be based upon the suspected underlying etiology of shock (eg, dobutamine for cardiogenic shock without significant hypotension, norepinephrine for septic and cardiogenic shock with hypotension, epinephrine for anaphylactic shock). (See 'Practical Issues' above and "Prognosis and treatment of cardiogenic shock complicating acute myocardial infarction", section on 'Vasopressors and inotropes'.)

● For patients with septic shock, we recommend norepinephrine as the first-line agent (Grade 1B). Alternative agents include epinephrine or, for patients with tachyarrhythmias, phenylephrine. Addition of a second or third agent should be individualized; vasopressin may be of benefit if the adrenergic agent is inadequate in those with hyperdynamic septic shock while an inotropic agent may be appropriate in those with hypodynamic septic shock. (See 'Adrenergic agents' above and 'Nonadrenergic agents' above and 'Choice of agent in septic shock' above.)

● Complications of vasopressor therapy include hypoperfusion (particularly affecting the extremities, mesentery or kidneys), dysrhythmias, myocardial ischemia, peripheral extravasation with skin necrosis, and hyperglycemia. (See 'Complications' above.)

Use of UpToDate is subject to the Subscription and License Agreement.

REFERENCES


Topic 1619 Version 22.0
## Vasopressors and Inotropes in Treatment of Acute Hypotensive States and Shock: Adult Dose and Selected Characteristics

<table>
<thead>
<tr>
<th>Agent</th>
<th>US trade name</th>
<th>Initial dose</th>
<th>Usual maintenance dose range</th>
<th>Range of maximum doses used in refractory shock</th>
<th>Role in therapy and selected characteristics</th>
</tr>
</thead>
</table>
| Norepinephrine (noradrenaline) | Levophed      | 8 to 12 mcg/minute (0.1 to 0.15 mcg/kg/minute) | 2 to 4 mcg/minute (0.025 to 0.05 mcg/kg/minute) | 35 to 100 mcg/minute (0.5 to 0.75 mcg/kg/minute; up to 3.3 mcg/kg/minute has been needed rarely) | - Initial vasopressor of choice in septic, cardiogenic, and hypovolemic shock.  
- Wide range of doses utilized clinically.  
- Must be diluted; eg, a usual concentration is 4 mg in 250 mL of D5W or NS (16 micrograms/mL). |
| Epinephrine (adrenaline)     | Adrenalin     | 1 mcg/minute (0.014 mcg/kg/minute)   | 1 to 10 mcg/minute (0.014 to 0.14 mcg/kg/minute) | 10 to 35 mcg/minute (0.14 to 0.5 mcg/kg/minute) | - Initial vasopressor of choice in anaphylactic shock.  
- Typically an add-on agent to norepinephrine in septic shock when an additional agent is required and occasionally an alternative first-line agent if norepinephrine is contraindicated.  
- Increases heart rate; may induce tachyarrhythmias and ischemia.  
- Elevates lactate concentrations during initial administration (ie, may preclude use of lactate clearance goal); may decrease mesenteric perfusion.  
- Must be diluted; eg, a usual concentration is 1 mg in 250 mL D5W (4 micrograms/mL). |
| Phenylephrine                | Neo-Synephrine, Vazculep | 100 to 180 mcg/minute until stabilized (alternatively, 0.5 to 2 mcg/kg/minute) | 20 to 80 mcg/minute (0.25 to 1.1 mcg/kg/minute) | 80 to 360 mcg/minute (1.1 to 6 mcg/kg/minute); Doses >6 mcg/kg/minute do not increase | - Pure alpha-adrenergic vasoconstrictor.  
- Initial vasopressor when tachyarrhythmias preclude use of norepinephrine. |
<table>
<thead>
<tr>
<th>Drug</th>
<th>Category</th>
<th>Dosage 1</th>
<th>Dosage 2</th>
<th>Dosage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>Inotropin</td>
<td>2 to 5 mcg/kg/minute</td>
<td>5 to 20 mcg/kg/minute</td>
<td>20 to &gt;50 mcg/kg/minute</td>
</tr>
</tbody>
</table>

- **Efficacy according to product information in the United States**

- **Alternative vasopressor for patients with septic shock who:**
  1. develop tachyarrhythmias on norepinephrine,
  2. have persistent shock despite use of two or more vasopressor/inotropic agents including vasopressin (salvage therapy), or
  3. high cardiac output with persistent hypotension.

- May decrease stroke volume and cardiac output in patients with cardiac dysfunction.

- May be given as bolus dose of 50 to 100 micrograms to support blood pressure during rapid sequence intubation.

- Must be diluted; e.g., a usual concentration is 10 mg in 250 mL DSW or NS (40 micrograms/mL).

- **A second-line agent to norepinephrine in highly selected patients (i.e., low risk of tachyarrhythmias or bradycardia induced hypotension).**

- More adverse effects (e.g., tachycardia, arrhythmias particularly at doses ≥ 20 mcg/kg/minute) and failed therapy than norepinephrine.

- May be useful in selected patients (e.g., with compromised systolic function or bradycardia at low risk for tachyarrhythmias).

- Lower doses (e.g., 1 to 3 mcg/kg/minute) should not be used for renal protective effect and can cause hypotension during weaning.

<table>
<thead>
<tr>
<th>Antidiuretic hormone</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vasopressin</strong> (arginine-vasopressin)</td>
<td><strong>Pitressin, Vasostrict</strong></td>
<td>0.03 units per minute (alternatively 0.01 to 0.03 units/minute initially)</td>
<td>0.03 to 0.04 units per minute (not titrated)</td>
<td>0.04 to 0.07 units/minute; Doses &gt;0.04 units/minute can cause cardiac ischemia and should be reserved for salvage therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Must be diluted; eg, a usual concentration is 400 mg in 250 mL DSW (1.6 mg/mL); use of a commercially available pre-diluted solution is preferred.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Add-on to another vasopressor (eg, norepinephrine) to augment efficacy and decrease initial vasopressor requirement. Not recommended as a replacement for a first-line vasopressor.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pure vasoconstrictor; may decrease stroke volume and cardiac output in myocardial dysfunction or precipitate ischemia in coronary artery disease.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Must be diluted; eg, a usual concentration is 25 units in 250 mL DSW or NS (0.1 units/mL).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inotrope (beta₁ adrenergic)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dobutamine</strong></td>
<td><strong>Dobutrex</strong></td>
<td>0.5 to 1 mcg/kg/minute (alternatively, 2.5 mcg/kg/minute in more severe cardiac decompensation)</td>
<td>2 to 20 mcg/kg/minute</td>
<td>20 to 40 mcg/kg/minute; Doses &gt;20 mcg/kg/minute are not recommended in heart failure and should be reserved for salvage therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Initial agent of choice in cardiogenic shock with low cardiac output and maintained blood pressure.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Add-on to norepinephrine for cardiac output augmentation in septic shock with myocardial dysfunction (eg, in elevated left ventricular filling pressures and adequate MAP) or ongoing hypoperfusion despite adequate intravascular volume and MAP.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increases cardiac contractility and rate; may cause hypotension and tachyarrhythmias.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Must be diluted; a usual concentration is 250 mg in 500 mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

https://www.uptodate.com/contents/use-of-vasopressors-and-inotropes/print?source=search_result&search=vasopressors&selectedTitle=1~150
**Inotrope (nonadrenergic, PDE₃ inhibitor)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Name</th>
<th>Loading Dose</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milrinone</td>
<td>Primacor</td>
<td>Optional loading dose: 50 mcg/kg over 10 minutes (usually not given)</td>
<td>0.125 to 0.75 mcg/kg/minute</td>
</tr>
</tbody>
</table>

- Alternative for short-term cardiac output augmentation to maintain organ perfusion in cardiogenic shock refractory to other agents.
- Increases cardiac contractility and modestly increases heart rate at high doses; may cause peripheral vasodilation, hypotension, and/or ventricular arrhythmia.
- Renally cleared; dose adjustment in renal impairment needed.
- Must be diluted; eg, a usual concentration is 40 mg in 200 mL D5W (200 micrograms/mL); use of a commercially available pre-diluted solution is preferred.

- All doses shown are for intravenous (IV) administration in adult patients. The initial doses shown in this table may differ from those recommended in immediate post-cardiac arrest management (ie, advanced cardiac life support). For details, refer to the UpToDate topic review of post-cardiac arrest management in adults, section on hemodynamic considerations.
- Vasopressors can cause life-threatening hypotension and hypertension, dysrhythmias, and myocardial ischemia. They should be administered by use of an infusion pump adjusted by clinicians trained and experienced in dose titration of intravenous vasopressors using continuous noninvasive electronic monitoring of blood pressure, heart rate, rhythm, and function. Hypovolemia should be corrected prior to the institution of vasopressor therapy. Reduce infusion rate gradually; avoid sudden discontinuation.
- Vasopressors can cause severe local tissue ischemia; central line administration is preferred. When a patient does not have a central venous catheter, vasopressors can be temporarily administered in a low concentration through an appropriately positioned peripheral venous catheter (ie, in a large vein) until a central venous catheter is inserted. The examples of concentrations shown in this table are useful for peripheral (short-term) or central line administration. Closely monitor catheter site throughout infusion to avoid extravasation injury. In event of extravasation, prompt local infiltration of an antidote (eg, phentolamine, if available) may be useful for limiting tissue ischemia. Stop infusion and refer to extravasation management protocol.
- Vasopressor infusions are high-risk medications requiring caution to prevent a medication error and patient harm. To reduce the risk of making a medication error, we suggest that centers have available protocols that include steps on how to prepare and administer vasopressor infusions using a limited number of standardized concentrations. Examples of concentrations and other detail are based on recommendations used at experienced centers; protocols vary.

D5W: 5% dextrose water; MAP: mean arterial pressure; NS: 0.9% saline.

*Data from:*

https://www.uptodate.com/contents/use-of-vasopressors-and-inotropes/print?source=search_result&search=vasopressors&selectedTitle=1~150
3. Lexicomp Online. Copyright © 1978-2016 Lexicomp, Inc. All Rights Reserved.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Receptor activity</th>
<th>Predominant clinical effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alpha-1 Beta-1 Beta-2 Dopaminergic</td>
<td>SVR ↑↑, CO ↔/↑ SVR ↑↑, CO ↔/↑ CO ↑↑, SVR ↓ (low dose) SVR↑ (higher dose)</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>+++ 0 0 0</td>
<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>+++ ++ 0 0</td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>+++ +++ ++</td>
<td></td>
</tr>
<tr>
<td>Dopamine (mcg/kg/min)*</td>
<td>0.5 to 2.</td>
<td>CO</td>
</tr>
<tr>
<td></td>
<td>+ + 0 ++</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. to 10.</td>
<td>++ + 0 ++</td>
</tr>
<tr>
<td></td>
<td>10. to 20.</td>
<td>++ ++ 0 ++</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>0/+ +++ ++</td>
<td>CO ↑, SVR ↓</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>0 +++ +++</td>
<td>CO ↑, SVR ↓</td>
</tr>
</tbody>
</table>

+++: Very strong effect; ++: Moderate effect; +: Weak effect; 0: No effect.
* Doses between 2. and 5. mcg/kg/min have variable effects.

Graphic 63100 Version 1.0
Use of vasopressors and inotropes - UpToDate

https://www.uptodate.com/contents/use-of-vasopressors-and-inotropes/print?source=search_result&search=vasopressors&selectedTitle=1~150

Close